X Chromosome Dosage Influences DNA Methylation Dynamics during Reprogramming to Mouse iPSCs.

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Public Summary:
By studying the differences between mouse embryonic stem cells and mouse adult cells, we have discovered that epigenetic modifications and not DNA mutations is responsible for the "embryonic state" of induced stem cells from adult tissue. Additionally, in female cells induced stem cells from adult tissue, both X chromosomes are reactivated by epigenetic changes.

Scientific Abstract:
A dramatic difference in global DNA methylation between male and female cells characterizes mouse embryonic stem cells (ESCs), unlike somatic cells. We analyzed DNA methylation changes during reprogramming of male and female somatic cells and in resulting induced pluripotent stem cells (iPSCs). At an intermediate reprogramming stage, somatic and pluripotency enhancers are targeted for partial methylation and demethylation. Demethylation within pluripotency enhancers often occurs at ESC binding sites of pluripotency transcription factors. Late in reprogramming, global hypomethylation is induced in a female-specific manner. Genome-wide hypomethylation in female cells affects many genomic landmarks, including enhancers and imprint control regions, and accompanies the reactivation of the inactive X chromosome. The loss of one of the two X chromosomes in propagating female iPSCs is associated with genome-wide methylation gain. Collectively, our findings highlight the dynamic regulation of DNA methylation at enhancers during reprogramming and reveal that X chromosome dosage dictates global DNA methylation levels in iPSCs.